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EXAMINER	
SAUCIER, SANDRA E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/808,880	WATKINS, STEVEN M.	
	Examiner	Art Unit	
	Sandra Saucier	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,10-12,14,22,26,27,32-34 and 61-66* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,11,12,14,22,26,27,32-34 and 61-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 8, 10-12, 14, 21, 22, 26, 27, 32-34, 61-66 are pending. Claims 1, 8, 11, 12, 14, 21, 22, 26, 27, 32-34, 61-66 are considered on the merits. Claim 10 is withdrawn from consideration as being drawn to a non-elected invention.

Election/Restriction

The elected species are directed to a method to determine if a pharmaceutical, nutritional, genetic, toxicological or environmental treatment, phenotypic state, regimen or dosage influences *de novo* fatty acid synthesis in liver tissue as determined from the quantization of palmitoleic or palmitic acid in the cholesterol ester fraction in plasma. Even though the elected species do not incorporate the ratio of palmitoleic/palmitic and the claims have been amended to have this new measurement in the methods, it has been permitted and an action on the merits follows.

Claim Rejections - 35 USC § 112

ENABLEMENT

Claims 1, 8, 11, 12, 14, 21, 22, 26, 27, 32-34, 61-66 remain/are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for assessing *de novo* fatty acid synthesis in a liver tissue (elected species) by quantifying a marker, which is either palmitoleic acid concentration or the ratio of palmitoleic acid to palmitic acid in the cholesterol ester fraction of blood. Further, the specification does not provide for a correlation with any pharmaceutical agent or appearance of a phenotypic state or environmental condition.

Platelets, red cells, leukocytes are all blood products. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

For example, one would not reasonably assume that *de novo* fatty acid synthesis in the liver could be assessed by sampling the fatty acid content of

platelets nor does the specification teach such relationships. However, this is the breadth of the independent claim.

Applicant has amended the claims to state that there is a correlating step. However, there is no disclosure or demonstration of whether there is a positive or inverse correlation between the purported marker in the cholesterol ester fraction of plasma and *de novo* synthesis in the liver.

Further, the specification does not teach a correlation between, for example the propensity for weight gain, genetic modification, etc.. And, no positive correlation of any condition or disease with any fatty acid "marker" appears to be demonstrated. Thus, the independent claim which is open to further steps or determinations encompasses associating menopause or ageing, for example, with CE fatty acid measurements, 16:1n7 or 16:1n7/16:0 as taught in the specification is not enabled.

The specification, while perhaps describing a methodology of complete lipid type and identity analysis and philosophical hypothetical predictions of usefulness or potential, fails to correlate any of the claimed, broad classifications with a consistent variation in cholesterol palmitoleate from the CE fraction of plasma with *de novo* fatty acid synthesis changes in the liver.

The state of the art with regard to a correlation between a weight gain or loss due to a nutritional treatment and a change in a marker of *de novo* fatty acid synthesis in a tissue as in one embodiment of the disclosed invention is undeveloped.

With regard to the claims where a method of determining whether a treatment will cause weight gain or loss, weight gain or phenotypic change is not only dependent on *de novo* fatty acid synthesis, but also on fatty acid oxidation. See Kusunoki *et al.* [U], "Modulation of Fatty Acid Metabolism as a ***Potential*** Approach to the Treatment of Obesity and the Metabolic Syndrome" (italics are mine).

Nutrition Reviews 1991 [V] states that there is no difference in *de novo* fatty acid synthesis due to non-insulin dependent diabetes, (page 255). Thus, in claim 42, for example, neither the specification nor the state of the art provides a correlation with propensity, risk or metabolic basis for diabetes.

De novo fatty acid synthesis is depressed in animals consuming a high fat diet; however, these animals may gain weight even though *de novo* fatty acid synthesis is depressed. An animal on a low-fat, high carbohydrate diet may have elevated *de novo* synthesis and weight gain, see the review by Parks *et al.* [W]. Thus, *de novo* fatty acid synthesis has not been shown to be correlated with the propensity, risk or metabolic basis for weight gain or loss either by the specification or the state of the art.

Guo *et al.* [X] teach that *de novo* lipogenesis under eucaloric or hypocaloric conditions occurs mainly in the liver, while under hypercaloric conditions adipose tissue is the site of appreciable *de novo* synthesis (discussion).

Thus, no consistent correlation has been taught by either the specification or the prior art between *de novo* fatty acid synthesis as measured by the mass or quantity or concentration of palmitic or palmitoleic acid in the cholesterol ester fraction of plasma and *de novo* fatty acid synthesis in the liver with any disease or phenotypic state or propensity for success in a treatment or even with applicants own tested drugs CL 316,243 or rosiglitazone, see analysis of the data below.

There is no unambiguous “correlation” with weight gain or with any disease process or even with *de novo* fatty acid synthesis in the liver that has been demonstrated. What has been demonstrated is that that when prediabetic mice are administered rosiglitazone, which has enhancing effects on liver FA synthesis, they have an elevated palmitoleic acid content in the cholesterol ester fraction of plasma or an elevated ratio of palmitoleic to palmitic acids. This is still not what is being claimed.

Further, the claim states that it is a method of assessing.... by quantifying.... The claim fails to state how the "quantifying" leads to or is correlated with the "assessing" which is required by the preamble. The specification fails to teach such a correlation with the palmitoleic or palmitoleic ration which is consistent over even applicants own examples of one drug which supposedly increases *de novo* FA synthesis in liver and a second drug which supposedly decreases de novo FA synthesis in liver according to applicants arguments.

The specification fails to teach what the specific correlation to the specific drug, disease state, risk or propensity or phenotypic state is and instead relies on the reader to form opinions as what the correlation or assessment might be. This is not enablement, but rather an attempt to claim a method in which any outcome would fall under its scope.

Undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

As set forth in In re Fisher, 427 F2.d 833, 839, 166 USPQ 18, 24 (CCPA) 1970: [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of the enablement varies inversely with the degree of unpredictability of the factors involved. Ex parte Humphreys, 24 USPQ2d, 1260.

INDEFINITE

Claims 61-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention.

It is unclear if the determination of the enzyme activity is considered to be the marker of *de novo* fatty acid synthesis in a tissue or if this is a further determination to be made in addition to the quantification of palmitoleic acid and palmitic acid. Please review the "wherein..." clause which does not appear to be the method as claimed in the independent claim.

Response to Arguments

Applicant presents some additional studies in a declaration in an attempt to show an unambiguous correlation of both CE16:ln7 and the ratio of CE 16:1n7/CE16:0 in the blood to the increase/decease of fatty acid synthesis in the liver.

The declaration was previously carefully considered with the following results.

Study A shows that db/db mice administered rosiglitazone have elevated plasma CE16:1n7. It appears that the leptin knockout, a genotype known to gain weight (db/db mice), do not have elevated plasma CE16:1n7 when not administered rosiglitazone even though these mice appear to show elevated FAS expression. Thus, while demonstrating that elevated CE16:ln7 and the ratio of CE16:1n7/CE16:0 is correlated with rosiglitazone administration to db/db mice, this experiment fails to demonstrate a correlation with any disease state or with weight gain or with FAS expression. Further, in the arguments on page 12, it is stated that rosiglitazone is a known inducer of *de novo* fatty acid synthesis in the liver and adipose tissue. However, this increase in FAS expression does not appear to be correlated with plasma CE16:1n7 in db/db mice or with plasma CE 16:1n7 in db/+ mice administered rosiglitazone in Exhibit 2.

Applicant argues that Study A demonstrates the positive correlation of both palmitoleic acid in cholesterol ester and the ratio of palmitoleic/palmitic in

plasma with the expression of FAS in liver. However, the statement that the administration of rosiglitazone to db/+ mice "... increased FAS was not observed" appears on page 4 of the declaration. This means that applicants argue on the one hand that rosiglitazone is a known enhancer of *de novo* fatty acid synthesis in the liver and should, therefore, be related to fatty acid synthetase levels, which has been accepted by the examiner, but on the other hand, the applicants now argue that administration of the heretofore argued enhancer, rosiglitazone to db/+ mice does not increase fatty acid synthesis. This appears to be a contradiction, which is not resolved by applicants arguments. Applicants have perhaps demonstrated that db/db mice when administered rosiglitazone show elevated FAS expression in liver and increased palmitoleic and palmitoleate/palmitate values in the CE fraction of plasma. However, this is not what has been claimed.

In exhibit 3, an undisclosed drug, said to be a PPAR gamma agonist (which is not rosiglitazone) was given to ZDF (Zucker diabetic fatty) rats in an undisclosed quantity for an undisclosed length of time. Weight gain and plasma CE16:1n7, CE 16:0 was measured in the rats over this undisclosed period of time. The Zucker diabetic fatty rats administered the undisclosed PPAR gamma agonist have elevated plasma CE16:1n7 and CE16:ln7/CE16:0 ratios and gained weight. However, all of the Zucker diabetic fatty rats gained weight, while only those administered PPAR gamma or PPAR delta agonist of undisclosed identity showed elevated CE16:1n7 levels. This experiment demonstrates at best, that Zucker diabetic rats all gained weight over the course of the experiment. Those administered PPAR gamma agonist of undisclosed identity gain more weight and have a higher plasma CE16:1n7 level. However, this does not establish a correlation that is unambiguous with weight gain, since all animals gained weight; however, not all animals exhibited elevated plasma CE16:1n7 levels. Thus, no consistent, clear correlation is shown between weight gain and plasma CE16:ln7 levels. These animals are also of a genetic type which develop obesity and diabetes, and thus all have a propensity for weight gain and diabetes, which does not appear to be correlated with elevated marker levels. Also, no measurement of FAS activity,

which may be argued to be an unambiguous indicator of increased *de novo* synthesis in liver, is shown.

Applicant argues that Exhibit 3 shows that Zucker diabetic rats which are treated with an undisclosed PPARY agonist which is not rosiglitazone show elevated markers in the CE fraction of plasma. There is no showing of increased liver fatty acid synthesis. There is no disclosure of what the compound administered is and whether it is recognized as a liver *de novo* fatty acid synthesis enhancer. This, once again is circular reasoning with regard to the relationship of the markers in plasma CE and the rate of synthesis in liver. Applicants postulate that elevation of CE 16:1n7 is an indicator of FA synthesis in liver, therefore, when this elevation is found, it follows that liver FA synthesis is elevated.

Study C is another study where rosiglitazone is administered to diabetic humans, which shows that rosiglitazone increases CE16:1n7 levels in plasma. No correlation is demonstrated between weight increases in the control (not administered rosiglitazone) and CE16:1n7 plasma levels or liver *de novo* synthesis is shown.

Applicant argues that rosiglitazone is a known enhancer of FA synthesis in liver, and its administration to diabetics then tested for plasma CE markers shows the correlation between these two. While this may be true, the applicants claims are not commensurate in scope with the claims. It appears that administration of rosiglitazone to diabetic humans, prediabetic mice, (pre)diabetic rats may increase markers in plasma CE. However, when administered to db/+ (normal phenotype) mice no such elevation in FA synthesis occurs. The compound appears to be an enhancer of FA synthesis in liver for (pre)diabetics alone since no positive results of administration in exhibit 2 for db/+ are seen.

Study D shows that under caloric restriction, of undisclosed degree, CE16:1n7 levels in plasma are decreased. It is difficult to understand how this

study is related to the claimed methods because the example is not related to the propensity, risk or metabolic basis for obesity or phenotype or environmental condition, procedure etc.. Nor is the example related to lipogenesis since at page 31 of the specification, it is stated that fasting increases de-novo lipogenesis in the liver. However, according to Study D, CE16:1n7 levels are decreased.

Applicants argue that fasting and severe caloric restriction are different nutritional interventions. Applicants urge that severe dieting results in loss of weight, and that during severe dieting the plasma CE markers are reduced. Then again, apply the circular reasoning that if the plasma CE markers are reduced, liver *de novo* FA synthesis is also reduced.

Response to Arguments

Applicant's further arguments filed 3/14/08 have been fully considered but they are not persuasive.

Applicant has amended the claims to state that the fluid sample is blood or a blood product. Please note that a suspension of platelets would be considered to be a fluid sample in the same way that blood which contains formed cellular elements is a fluid. However, the specification is not enabled for such a sample, nor is such as sample contemplated in the specification. Applicants argue that one of skill in the art would know that the markers of *de novo* fatty acid synthesis would not be quantified from a cellular component of blood. However, applicants do not amend their claims to be limited to plasma, which is what has been exemplified. Attention to what has been shown might further prosecution.

Applicants argue that rosiglitazone is a known enhancer of *de novo* FA synthesis in the liver and present a reference, Oakes *et al*.., which incidentally does not mention rosiglitazone.

In summation there are three main points to be addressed.

First, are the effects of the administration of the drugs rosiglitazone and CL 316,243 known to effect the rate of *de novo* fatty acid synthesis in liver or not in the absence in the specification of the classic indicators such as fatty acid synthetase activity/induction, labeled glucose, acetate incorporation rates into FA.

Oakes *et al.* teach that thiazolidinediones generally raise FA synthesis in liver. Later references confirm that rosiglitazone increases FA synthesis in liver in at least diabetic rodents. Therefore, it is accepted for the sake of argument by the examiner that one of the many effects of such an administration of rosiglitazone is the increase of *de novo* fatty acid synthesis in the liver, even in the absence of evidence in the specification through classical assays that rosiglitazone does indeed have an enhancing effect on this pathway in the liver in normal as well as (pre)diabetic animals.

CL 316,243 is stated by applicant to be an inhibitor of *de novo* FAS in liver. However, no classic measure of such decreased synthesis are demonstrated such as FA synthetase induction/activity, glucose, acetate incorporation into FA, for example. The only support for this statement appears to be the circular logic which postulates that because CL 3316243 administration shows decrease 16:1n7 concentration in cholesterol ester of plasma, it, therefore, must be a FAS inhibitor in liver.

Second, is the question of the significance of the data. Administration of rosiglitazone to prediabetic male mice, has a positive correlation with increase in concentration of CE 16: 1n7 and with the ratio of the concentrations CE16:ln7/CE 16:0 in all lipid classes in the liver. In the CE fraction of plasma, an increase in 16:1n7 is found (114.1 to 200.8). Also, the ratio of CE 16:1n7/CE 16:0 is increased from 0.813 to 1.78. these appear to be significant in the case of rosiglitazone to prediabetic male mice (5 in the group).

Administration of the purported inhibitor of fatty acid synthesis in liver, CL 316, 243 on the other hand, does not produce consistent, unambiguous

correlations with the CE plasma "markers" of fatty acid synthesis in the liver.

In example 2, CL 316,243 is administered to NON mice (normal?). The plasma cholesterol palmitate content in the control is 144.8±7.0 and decreases to 114.4± 10.3 in the treated mice, while the 16:ln7 content of plasma cholesterol esters is 228.6±23.2 and decreases to 84.9± 31.5 in the treated group.

The ratio of palmitoleic/palmitic in the cholesterol ester fraction of plasma in example 2 goes from 1.578±0.112 in the control to 1.347± 0.285 which has been calculated by 228.6/144.8=1.578 and 114.4/84.9=1.347. The standard deviations have been calculated by squaring the fractional deviations, adding them and taking the square root of the sum as follows.

sqrt $(23.2/228.6)^2+ (7.0/144.8)^2 =0.1124$ which is the standard deviation of the ratio of the control plasma cholesterol ester fraction palmitoleic/palmitic.

Please note that the ranges of the ratios within their standard deviations overlap to a significant extent. That is, 1.578± 0.112 in the control in comparison to 1.347± 0.285 in the CL 316,243 treated mice does not appear to be a significant difference.

One can expect a the variation around the mean in any group which can be expressed by the standard deviation value. Thus, values from 1.578-0.112 to 1.578+0.112 yields a range of 1.466 to 1.69 for control ratio values, while the CL 316,243 treated mouse plasma ratio is 1.062 to 1.632. This does not appear to be a statistically significant variation in the ratios of palmitoleic to palmitic acids in the cholesterol ester fraction of plasma as a marker under the test conditions which the applicant urges is a reduction in *de novo* fatty acid synthesis in the liver.

In short, the specification fails to show that there is a consistent,

unambiguous correlation between *de novo* total fatty acid synthesis in the liver and the urged markers of palmitoleic/palmitic acid and the palmitoleic acid content of the cholesterol ester fraction in plasma (mass or accumulation or concentration) during administration of the two purported exemplars of increased and decreased FAS in liver, rosiglitazone and CL 316,243. Unambiguous may be interpreted to be a consistently statistically significant difference.

Third, has a correlation been demonstrated for phenotype, genetic modification, propensity for weight gain, etc., especially with regard to humans.

There is absolutely no evidence in the specification that these measurements of CE type, ratios in plasma and the purported correlations have any bearing on fatty acid synthesis in the liver in free living, normal humans. One of the many problems being that variations, for example in diet, such as amounts consumed of carbohydrate, high fat, unsaturated fats among other things all have effects on lipogenesis, see Kersten IDS. Thus, at the very least, diet must be tightly controlled if effects on other parameters are to be relevant to the condition desired to be further correlated with CE 16:1n7 or CE 16:1n7/16:0 in plasma. This element is not even considered in the present specification, yet the independent claim is open to humans as the source of the samples.

Also, there is no positive linkage of for example weight gain to increased *de novo* FA synthesis in liver. Weight gain may be a consequence of the type of diet, even though *de novo* synthesis of fatty acids is not increased in the liver, see Parks *et al.* and Guo *et al.* above. Weight gain may be a consequence of treatment with a therapeutic agent, nutritional regime, genetic modification, etc. and may be considered to be a phenotypic state. Also, the independent claim is open to such further correlations such as a predictor of weight gain/loss as described in the specification.

In short, the applicant has not claimed what has been demonstrated and

applicants arguments are therefore, not commensurate in scope to the showing.

No claims are allowed.

Conclusion

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed. Applicants should also keep in mind the elected species when amending claims and in arguments.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday, Tuesday, Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-

9197 (toll-free).

/Sandra Saucier/
Primary Examiner
Art Unit 1651